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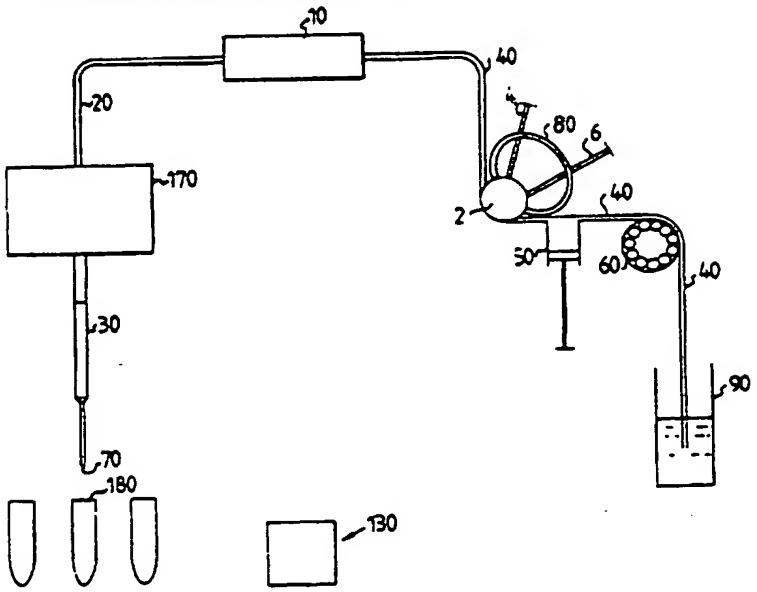

(57) Abstract

The invention relates to a method of analyzing liquid substances with the aid of a throughfl w detector (10) and a reagent. A substance sample volume is introduced into a sample tube (20) through the medium of a supply tube (30) and the sample volume and a reagent volume are mixed together and caused t react with one another and then transported to the detector (10) for analysis purposes. The sample volume and agent v lume are introduced into the sample tube (20) through an orifice (70) in the supply tube (30), immediately after one an ther. 'i .: sample volume and reagent volume are intermixed in the supply tube (30), and possibly also in the sample tube (20), with the aid of an air segment which precedes the sample and reagent volumes. The invention also relates t apparatus for carrying out the method, and to a supply tube particularly designed for use with such apparatus.

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Method for analysis and device for carrying out the method

The present invention relates to a method of chemically analyzing liquid substances with the aid of at least one throughflow sensor or detector, hereinafter referred to as "a detector", and at least one reagent, wherein a sample volume of the liquid substance to be analyzed is introduced into a flexible tube through a supply tube and the sample and a volume of reagent are mixed and caused to react with one another, and then transported through the flexible tube to the detector. The invention also relates to analysis apparatus designed to carry out the method, and to a supply tube which is adapted particularly for use with such apparatus.

The analysis method is preferably a batch-wise method and is mainly intended for use in clinical applications, such as in connection with intensive care, surgery, transplantations and other clinical applications where continuous monitoring of the chemical-physiological values of patients is required. The method is particularly suited for use when only a relatively few samples are to be analyzed, for instance in the analysis of samples taken from one or a few bed-ridden patients in a hospital ward.

Many different types of analysis apparatus are known to the art. In principle, these apparatus can be divided into two main groups: continuous analyzers and batch-wise working analyzers (hereinafter referred to as batch-analyzers).

In the case of continuous analyzers, the various samples are drawn by suction from their resp ctive contain rs into a tube in which the samples are moved in mutually one and the same direction throughout the entire analysis procedure. In this way, the samples form a continuous flow to which reagent is introduced at predetermined points, either batch-wise or

continuously. The flow of liquid finally reaches the measuring cell in which the liquid is assayed. All liquid transports in continuous analyzers are regulated with the aid of pumps, generally rotating displacement pumps, which also effect the outfeed of the samples. In turn, continuous analyzers can be divided between those in which the various samples in the tube are mutually separated, segmented, with the aid of air bubbles for instance, and those in which the samples in the tube constitute delimited liquid plugs in essentially laminar liquid carrier flows, which may possibly contain a reagent. These latter analyzers are said to work in accordance with the so-called Flow Injection Analysis, or the FIA principle. One problem with continuously working analyzers is that the reagent or reagents is/are introduced through separate supply tubes, valves, pumps, etc., which requires a complicated apparatus construction. Another problem associated with continuous analysis methods is, of course, the risk of contamination between the samples.

A continuous analysis method and system are known from US-A-4,853,336, wherein successive liquid segments containing related components in a liquid packet in which an analysis mixture is established for instance, are mutually separated by at least one immiscible segment, for instance air. These liquid segments are mixed within the apparatus at a later point in time, somewhere in a transport line, such as to achieve delayed on-line mixing of the various components. Mixing of the various components is achieved by either eliminating, fragmenting or physically removing the immiscible segment at selected sites along the line. In order to prevent the samples contaminating one another, an immiscible liquid is used to cover the inner surfaces of the apparatus and the outer surface of the probe.

Separate zones are provided for the removal of the air segments that separate the samples, so as to enable the components to mix together.

The risk of contamination is less serious in batch-analyzers on the other hand, since the samples are contained in individual containers during the analysis procedure. Reagents are added to the samples either before placing the containers in the analyzer, or in conjunction with transporting the containers through the analyzer. The containers finally reach the actual analyzing part of the apparatus, in which a part of the samples is drawn by suction from the containers and passed to an analysis assay cell. Upon completion of the sample assaying process, the cell is washed with a washing solution. One problem with batch-analyzers resides in the additions of reagent to the system and its admixture with the sample. This is a time-consuming process and is either carried out manually or automatically, although in separate working steps in all cases. The batch analyzer containers generally function as measuring cells in themselves, for instance cuvettes in different types of photometers, therewith obviating the need to transport part of the sample-reagent mixture to a separate measuring analyzer cell. One drawback with known batch processes is that relatively large quantities of sample and reagent are required. The amount of sample available must be at least sufficient to produce in practice a sample-reagent mixture in which the ratio between sample and reagent quantities is well adjusted. It is very difficult to attain acceptable precision with regard to this ratio when small quantities of sample are used. Furthermore, because the sample-reagent mixture is contained in a more or less open container from the time of being mixed to the actual time of assaying the sample, the mixture is more sensitive to evaporation in the case of smaller volumes. When the container itself forms a measuring cell, i.e. a cuvette, the problem is made worse because cuvettes must be relatively large and thus require relatively large volumes of sample-reagent mixture in order to cover the beam path in the photometer and therewith prevent stray light reaching the detector of the analyzer, this problem being well known in this particular technical field.

Concentration determinations performed with the aid of batch-analyzers are normally either end-point analyses or kinetic assays. End-point analyses involve recording the value at which the sample has ceased to react with the reagent, i.e. when said value is constant in a sufficient number of mutually sequential analyses. The measured value is related directly to the original sample concentration. When the reaction rate between sample and reagent is low, it will, of course, take a long time to perform the analysis. Provided that the reaction is not of the 0th order, a kinetic assay can then be carried out, i.e. a procedure in which the values obtained with a plurality of mutually sequential analyses are recorded and the derivative of the time-dependent curve described by said values calculated. The original concentration of the sample can then be calculated from the derivative and the initial concentration in the sample volume.

Batch-analyzers that include cuvettes are often designed to be placed in carousel-like devices by means of which the individual cuvettes are moved into the beam path of the detector. The devices operate in accordance with process sequences, analysis cycles (generally of a 25-30-second duration), in a number of steps, including among others:

- Washing sample pipettes
- Washing reagent pipettes
- Revolving the cuvette carousel for sample analysis/ assaying
- Pipetting samples with sample pipettes
- Pipetting reagents with reagent pipettes
- Rotating the cuvette carousel to bring forward an empty cuvette to be filled with sample and reagent
- Supplying the cuvette with sample
- Supplying the cuvette with reagent
- Mixing sample and reagent in the cuvette

and other necessary steps, such as moving sample and reagent to different positions, for instance. The large number of working steps required take considerable time to complete with each sample. The time taken to analyze each individual sample can be reduced by performing the steps in parallel to the greatest possible extent, i.e. by analyzing a plurality of samples in parallel, the time taken being the total analysis time divided by the number of samples. Expressed mathematically, this is

$$A=\frac{M}{p}*(p+m-1) \qquad (1)$$

where A is the total analysis time in relation to the number of samples,

M is the time taken for one analysis cycle,

m is the number of analysis cycles for each sample, and

p is the number of samples.

It will be immediately evident from the formula (1) that the analysis time per sample decreases quickly with the number of samples. Conversely, the analysis time is relatively long when only a few samples are to be analyzed.

Generally, when working in a clinical environment, for instance a hospital, the lowest possible noise level is desired. Batch-analyzers intended for clinical applications are encumbered with noise problems, because the large number of steps involved by the analyzing cycles unavoidably generate sound. It is therefore practically impossible to use an analyzer in the same room as bed-ridden patients in accordance with known techniqu s, because the noise l vels generated are not compatible with good nursing conditions.

Both end-point analyses and kinetic analyses can be made with this type of analysis apparatus. In the case of end-point assays, the values are determined over the number of measuring cycles require to obtain a constant value. In the case of kinetic assays, values are determined over a given, predetermined number of measuring cycles, whereafter the derivative of the change in concentration is calculated on the basis of the results obtained. Generally, from seven to ten measuring points are required to achieve sufficient precision in the calculations.

It follows from this that it would be natural to place a known analyzer used in hospitals, in a centrally located laboratory to which samples are transported from the various hospital wards. By analyzing as many as possible of the samples taken in the hospital in one and the same analyzer in the centrally located laboratory, the patients will be protected from noise disturbances and each sample will be analyzed in the shortest possible time. One problem with this procedure is that monitoring of the values of individual patients becomes complicated, because samples and the results of sample analyses must be interchanged between patient, laboratory, doctor and some other member of the hospital staff in accordance with planned administrative procedures, which increases the risk of error.

An overlying object of the present invention is to provide a method of analysis which enables the construction of simpler analysis apparatus in comparison with known techniques.

A particular object of the present invention is to provide a method of analysis which enables very small sample quantities to be analyzed without risk of contamination between the sample quantities.

Another particular object of the invention is to provide a method of analysis which when working with a relatively small number of samples will enable each sample to be analyzed in a much shorter time than that possible when practicing known techniques.

Still another object of the invention is to provide analytical apparatus suitable for use in clinical applications, and primarily apparatus which can be set-up and used in the proximity of patients to enable their chemical-physiological values to be monitored continuously.

The aforesaid overlying objects of the invention are achieved with the aid of an analysis method of the kind defined in the introduction in which the sample volume and the reagent volume are supplied to the analytical apparatus one after the other through an opening in the supply tube, and in which the sample quantity and the reagent quantity are mixed together in the supply tube, and optionally also in the flexible sample tube, through the medium of an air segment which precedes the sample and reagent volumes. The sample and reagent volumes are thus introduced immediately after one another in the absence of an intermediate air segment.

Naturally, air will be present downstream of or behind the sample and reagent volumes, meaning that the sample and reagent volumes will constitute a coherent package between two air segments.

It has surprisingly been found that sample and reagent can be mixed together satisfactorily in this simple fashion. One explanation may be that eddies are generated in liquid at the liquid-air segment interface and move outwards and then downwards along the full length of the liquid plug and therewith cause the contents of the full plug (i.e. the combination of sample and reagent) to mix together. In principle, this mixing phenomenon is independent of whether

the liquid flow is turbulent or laminar. However, the mixing effect can be optimized by selecting suitable values for parameters that are relevant with regard to liquid flow in tubes or pipes, for instance such parameters as flow rate, hydraulic diameter, roughness of the tube surface, individual resistance, viscosity of the liquid flow, etc.).

The method according to the present invention is also effective in causing sample and reagent to mix together surprisingly quickly; the sample and reagent are mixed together in the time taken for them to move from the supply tube to the detector, which means a time consumption of up to about two seconds, generally about one second.

Because the sample and reagent can be supplied in this simple manner while satisfactorily mixing the sample and reagent together, the analytical apparatus used may be given a simpler construction, since only one supply tube is required for the supply of both sample and reagent. Naturally, this will present to the person skilled in this art the possibility of making other obvious constructional simplifications.

In one preferred embodiment, the method is a batch method. This provides a method which enables very small volumes of sample to be analyzed without risk of contamination between the volumes. Although the risk of contamination is reduced because the method is of the batch kind, the possibility of working with small sample quantities is obtained with the aid of the present invention by virtue of the fact that sample and reagent are mixed precisely as they are supplied to the analytical apparatus. This enables small sample and reagent volumes to be taken-up with great precision and without risk of the mixing ratio being impaired by evaporation, because the sample and reagent volumes are mixed immediately prior to being assayed and are also protected within a tube or a

flexible tube from the point at which they are mixed to the location of the cell.

In one particularly preferred embodiment of the inventive method, which is of the batch kind, the detector, the flexible tube and the supply tube are washed clean with washing solution after the assaying process, said washing solution being supplied to the detector through a washing tube and thereafter through the detector, whereafter the washing solution is flushed through and out of the supply tube via said flexible tube. In this way, there is obtained a method which, in principle, solely comprises the following steps:

- Washing the analyzing cell and the supply tube.
- Sucking-up air (for air segmentation).
- Sucking-up sample (or reagent).
- Sucking-up reagent (or sample).
- Simultaneous mixing of sample and reagent and transportation of the mixture to the analyzing cell.
- Analysis/assay.
- Followed possibly by a fresh wash and sucking-up air and a fresh sample.

In comparison with the number of working steps that are included in conventional batch processes (see above), it will immediately be seen that less noise will be generated and that the time taken to analyze each sample is considerably shortened by the novel method. Because the working steps are carried out serially, the time taken to analyze each sample will be constant, i.e. the time does not change with the number of samples. In the case of kinetic analyses effected in accordance with the inventive method, the time taken to analyze each sample is about one minute. It is a simple matter to show with the aid of the equation (1) that kinetic analyses effected in accordance with the inventive method are much quicker than kinetic analyses that are effected in

inventive method is quicker than conventional batch methods that operate in parallel with many samples simultaneously, when a few samples require analysis over a longer analysis period. When taken together, it will be seen that an inventive batch method is much better suited for such analytical processes when only a relatively few samples are to be analyzed and a quick result of the analyses is required, e.g. when analyzing samples taken from one or a few bed-ridden patients in a hospital ward.

The present invention also relates to apparatus for carrying out the inventive method, said apparatus including at least one detector, a detector-connected flexible tube, a supply tube having a first free end and a second end connected to said flexible tube, further a washing tube connected to the detector, and at least one pump for pumping liquid substance and liquid reagent into and out of the detector respectively and for pumping washing solution through the washing tube, the detector, the sampletubeand the supply tube, said supply tube having an opening through which sample and reagent can be supplied sequentially one after the other. The supply tube is preferably configured for mixing of sample and reagent therein, and optionally also in the following sample tube.

In one preferred embodiment of the apparatus, the supply tube has at least two throughflow areas of mutually different size, wherein the smaller throughflow area merges with the larger throughflow area via an abrupt increase in area in a direction from said first end and towards said second end, and wherein the abrupt increase in area is intended to assist in generating eddies or turbulence in the flow in the supply

tube and possibly also in the sample tube, at least in a direction from the first end of the supply tube and towards its second end downstream of the abrupt increase in area.

According to one particularly preferred embodiment, the apparatus is a batch analyzing apparatus and is provided with a metering pump for pumping liquid substance and reagent to the detector, and a washing pump which pumps washing solution from a washing solution container into the detector through the washing tube, and from there out through the supply tube via said tube, wherein the metering pump is an oscillating displacement pump, e.g. a plunger pump or injection pump, and is connected to the washing tube at a location between the detector and the washing pump, and wherein the washing pump is a rotary displacement pump, e.g. a peristaltic pump. This embodiment provides a batch analyzing apparatus of particularly uncomplicated design in comparison with conventional apparatus. The particular combination of pumps eliminates at one stroke a large part of the requirement of valves and like devices with which known techniques are encumbered. This is described in more detail below. The apparatus is also suitable for use in clinical applications, particularly as it can be set-up and used in the proximity of patients for the purpose of monitoring continuously their chemical/physiological values, this being achieved by virtue of the apparatus working with relatively few steps with each sample and therewith generating relatively little noise.

According to another embodiment of the apparatus, the apparatus includes a sample loop which is connected either to the flexible sample tube or to the washing hose, said sample loop being provided with valves for activating and deactivating the sample loop so as to alternate the flow in the analysis apparatus and the flow in an external analysis apparatus, which may be a chromatographic device, e.g. an HPLC-apparatus.

The present invention will now be described in more detail with reference to the accompanying drawings, in which

Fig. 1 illustrates schematically one embodiment of an inventive apparatus;

Fig. 2 is a cross-sectional view of part of the supply tube of the apparatus shown in Fig. 1; and

Fig. 3 illustrates a method of washing the supply tube.

The apparatus illustrated in Fig. 1 is used by first pumping washing solution from a container 90 for washing solution through a flexible washing tube 40 with the aid of a washing pump 60, in the illustrated case a peristaltic pump. The washing tube of the illustrated apparatus is made of PVC plastic. The washing solution is pumped through the washing tube 40, a photometric detector 10, and a sample tube 20 and out through an outlet orifice 70 of the supply tube 30 at a flow rate of about 50 µl/s. The sample tube 20 is made of PEEK plastic, because PEEK has a relatively low hydrophobicity which counteracts the adhesion of large air bubbles to the sample tube. However, other plastics having similar properties may be used as an alternative. The outer surface of the supply tube 30 is cleaned during the washing process with the aid of the washing vessel 130 (described in more detail with reference to Fig. 3). After being washed, the supply tube 30 is lifted from the washing vessel with the aid of a device 170 intended herefor and the apparatus is then ready for renewed analysis of samples. The device 170 moves the supply tube vertically and laterally, in this case in the plane of the drawing, and moves a stand for test tubes 180 in a direction perpendicular to the plane of the drawing. After having filled the supply tube 30 with washing solution, about 1 µl of air is first sucked into the supply tube 30 with the aid of the metering pump 50, which in the illustrated case is a plunger pump or injection pump. The

static peristaltic pump 60 functions therewith as a sealing valve, because it prevents liquid from passing through the washing tube 40. The device 170 then moves the supply tube 30 to the vicinity of and down into a test tube 180, which in the illustrated case is of the kind described in the Swedish Patent Application 9303344-7, i.e. a test tube provided with a rubber septum and a capillary tube for taking-up very small volumes of sample at the tube orifice. Samples (about 0.1-2.0 µl) are sucked into the supply tube 30 through its orifice 70, with the aid of the pump 50. After having moved the supply tube 30 to a reagent container (not shown), reagent (about 15 µl) is drawn correspondingly into the supply tube 30, through its orifice 70. The sample and reagent plugs are thus in contact with one another as they are pumped further through the tube 20 at a flow rate of about 5-50 µl/s (which in the case of the internal diameter of the tube corresponds to a speed of about 4-40 cm/s). Mixing of the sample with the reagent is begun in the supply tube 30 by virtue of air-segmenting. The supply tube 30 includes an abrupt change in area, as described in more detail below with reference to Fig. 2, which also possibly contributes further towards the intermixing of sample and reagent. The combined liquid plug will be sufficiently mixed for analysis purposes when located in the photometric detector 10. In the illustrated case, the detector 10 is of the kind described in SE-B-455 134, i.e. it comprises a thin tube of transparent material in which the mixture is contained, and light is passed through the cylindrical wall of the tube at an acute angle to the longitudinal axis thereof and is totally reflected within the tube one or more times and thereafter led out through said cylindrical surface at an acute angle. The illustrated embodiment is effective in achieving a kinetic analysis of the sample-reagent mixture in less than about thirty seconds, with the aid of the detector 10 and a computer (not shown) connected thereto, whereafter the mixture is washed from the apparatus with the aid of the washing pump 60 and the analysis sequence is

recommended. The full sequence takes about one minute. The apparatus illustrated in Fig. 1 is suitable for assaying such substances as glucose, lactate, glycerol, pyruvate, urea, creatinine, alcohols, glutamate and carbon dioxide. Analyses can also be carried out with an external analytical apparatus, e.g. an HPLC apparatus, for analyzing amino acids, purines, lactates, pyruvates, ascorbates, histamines, polyamines, leukotriens, free radicals, ions or selected pharmaceutical preparations, with the aid of a six-port valve 2 fitted to the washingtube40. The valve 2 is a two-position valve retailed under product number C6W by Valco Instruments Co., Houston, Texas, U.S.A. and functions to connect a sample loop 80 with the tube 40 when the valve 2 is set to a first position, therewith enabling the loop to be filled with sample-reagent mixture with the aid of the metering pump 50, while the sample loop 80 remains in contact with an HPLC apparatus (not shown) via the lines 4 and 6 when the valve 2 is set to a second position, so as to enable the sample-reagent mixture in the sample loop to be transferred to the HPLC apparatus.

As will be seen from Fig. 2, the supply tube 30 of the illustrated embodiment comprises two parts, i.e. a pointed cannula 100 and a tube 110. The cannula 100 is of the kind described in Swedish Patent Application 9303344-7 and has an outer diameter of only 0.4 mm and is particularly suitable for taking-up very small sample volumes from so-called microdialysis test tubes, as described in said Swedish patent application. The cannula 100 has an inner diameter of only 0.15 mm which, in combination with the injection pump 50 enables sample volumes as small as 0.1 μl to be taken-up with great precision. The cannula 100 terminates in the tube 110 at an abruptly increased area or section 120 and is attached to the tube in said area. As the inner diameter of the tube 110 is 0.4 mm, this increase in area will be slightly more than 600%, and will contribute towards intermixing of the sample and reagent.

Fig. 3 illustrates washing of the outer surface of the supply tube 30 with washing solution contained in a known washing vessel 130. The washing solution exiting from the supply tube 30 fills the space 140 and flows over the space-defining wall 150, as indicated by the arrows in the Figure. The outer surface of the supply tube 30 is therewith washed clean. The washing solution then exits through the outlet 160.

It will be understood that the scope of the present invention as described and illustrated includes several embodiments other than that described. The scope of the invention is therefore limited solely by the content of the following Claims, and by further developments made on the basis thereof.

CLAIMS

1. A method of chemically analyzing liquid substances with the aid of at least one throughflow sensor or detector (10), and at least one reagent, wherein a sample volume of the liquid substance is introduced in a sample tube (20) through the medium of a supply tube (30), and the sample volume and reagent volume are mixed together and caused to react with one another, whereafter the reaction mixture is transported through the sample tube (20) to the throughflow sensor or detector (10) for analysis purposes, **characterized** by
- introducing a first air segment into the sample tube (20);
- introducing the sample volume and reagent volume in the sample tube (20) into the supply tube (30) through an inlet orifice (70) sequentially one after the other; and
- immediately thereafter introducing a second air segment, wherein the sample volume and the reagent volume are caused to intermix as they flow through the supply tube (30) and optionally also through the sample tube (20) up to the throughflow sensor or detector (10).

2. A method according to Claim 1, **characterized** in that the sample volume and reagent volume held together by the two air s gments are mixed together in the supply tube (30) by virtue of eddies that are generated in the flow of sample and reagent in the supply tube (30) through the medium of the air segment, and possibly also in the flow in the sample tube (20).

3. A method according to Claim 1, **characterized** by the sample volume and reagent volume held together by the two air segments being intermixed in the supply tube (30) by virtue of segment-generated lateral and/or rearwardly directed laminar currents in the flow of sample and reagent in said supply tube (30), and possibly also in the flow in the sample tube (20).

4. A method according to any one of Claims 1-3, wherein the throughflow sensor or detector (10), the sample tube (20) and the supply tube (30) are through-washed with a washing solution subsequent to the completion of an analysis, **characterized** by passing the washing solution to the throughflow sensor or detector (10) through a washing tube (40) and thereafter through the throughflow sensor or detector (10), and thereafter passing the washing solution through and out of the supply tube (30), through the medium of the sample tube (20).

5. Apparatus for the automatic chemical analysis of liquid substances with the aid of at least one reagent, said apparatus comprising at least one throughflow sensor or detector (10), a sample tube (20) connected to the throughflow sensor or detector (10), a supply tube (30) having a first free-end and a second end which is connected to the sample tube (20), and further comprising a washing tube (40) connected to the sensor or detector (10), at least one pump (50, 60) for pumping liquid substance and reagent to and from the sensor or detector (10), and for pumping washing solution through the washing tube (40), the sensor or detector (10), the sample tube (20) and the supply tube (30), **characterized** in that the

- supply tube (30) has an orifice (70) intended for supplying sample and reagent in a sequence one after the other;
- a metering pump (50) for pumping a sample volume of liquid substance and reagent to the throughflow sensor or detector (10); and in that
- the apparatus further includes a washing pump (60) which functions to pump, via the washing tube (40), washing solution from a washing solution container (90) into the sensor or detector (10) and from there out through the supply tube (30), via the sample tube (20).

supply tube (30) is configured so that sample and reagent will be intermixed in the supply tube (30) and possibly also in the sample tub (20).

7. Apparatus according to Claim 5 or Claim 6, **characterized** in that the supply tube (30) has at least two throughflow areas which are of mutually different size, wherein the smaller throughflow area merges with the larger throughflow area via an abrupt increase in area in a direction from said first end towards said second end, wherein the abrupt increase in area is intended to assist in the generation of eddies or vortices in the flow in the supply tube (30), and possibly also in the sample tube (20), at least in a direction from said first end of the supply tube towards its second end, downstream of said abrupt increase in area.

8. Apparatus according to any one of Claims 5-7, **characteriz d** in that the metering pump (50) is an oscillating displacement pump and is connected to the washing tube (40) at a location between the sensor or detector (10) and the washing pump (60); and in that the washing pump (60) is a rotary displacement pump.

9. Apparatus according to any one of Claims 5-8, **characteriz d** in that the supply tube includes a cannula (100) whose longitudinal axis curves in the proximity of the cannula tip; in that the cannula tip is ground obliquely so that the plane of said tip intersects the tangent to the outer surface of the cannula tip (100) at its outer generatris furthest r moved from the centre of curvature and at a point which lies approximately central of the extension of the centre axis of the rectilinear part of the cannula (100).

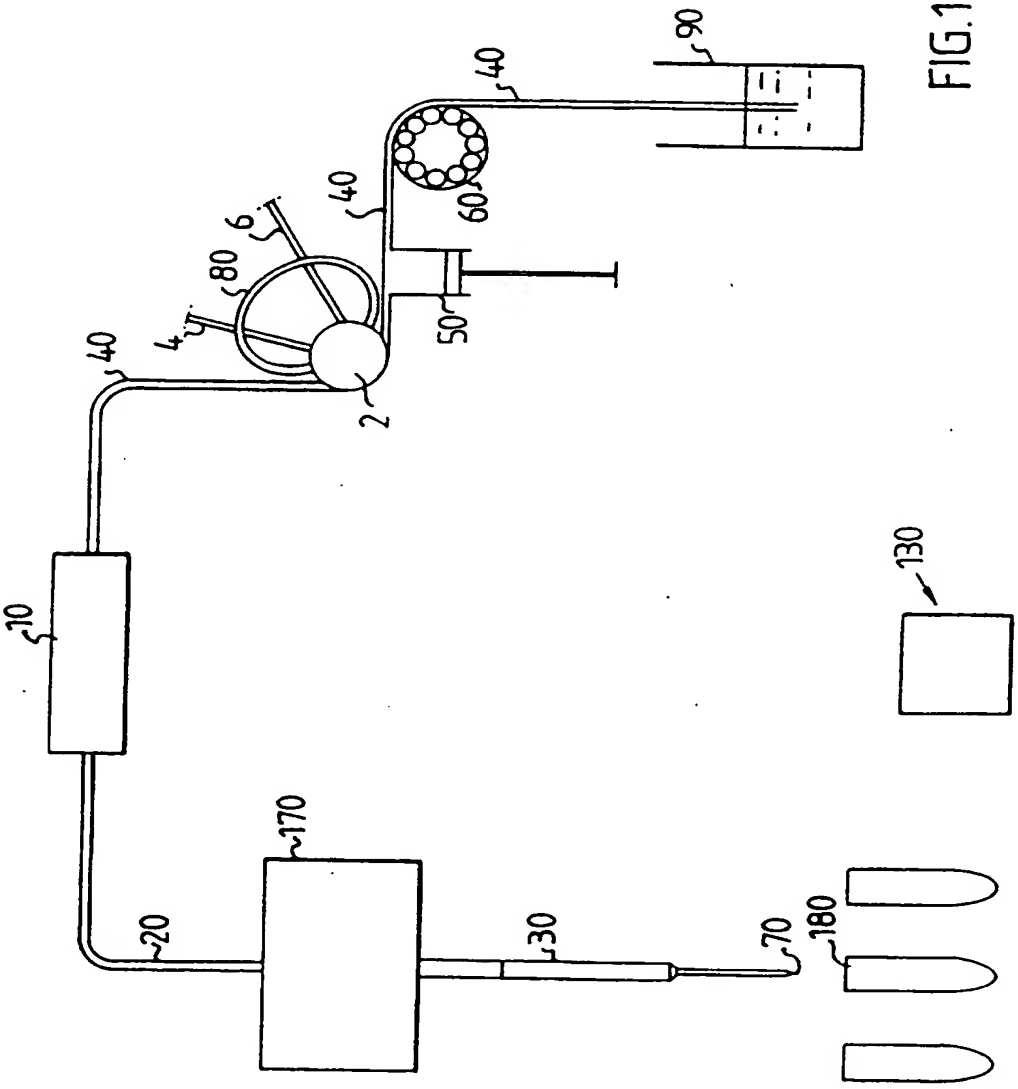

FIG.1

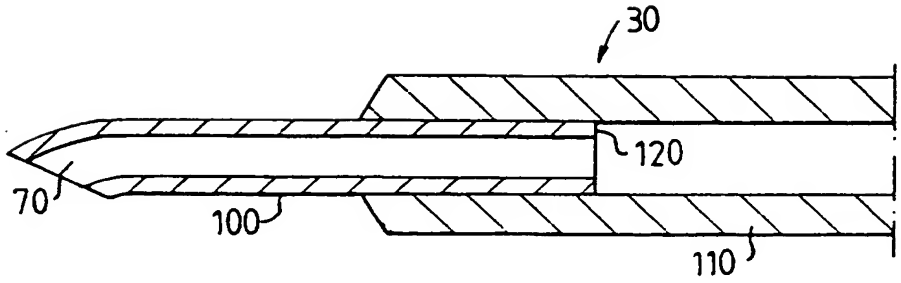

FIG. 2

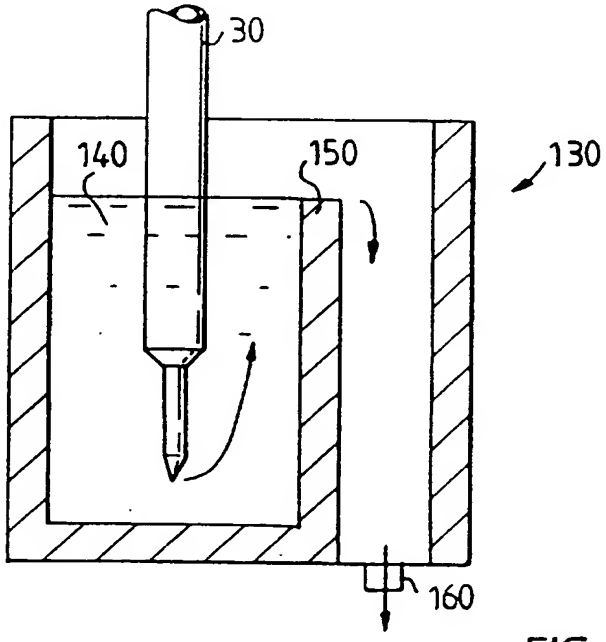

FIG. 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 95/01038

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: G01N 35/08
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum d· ıtation searched (classification system followed by classification symbols)

IPC6: G

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4853336 A (STEPHEN SAROS ET AL), 1 August 1989 (01.08.89), column 2, line 51 - column 3, line 22; column 5, line 1 - line 21; column 5, line 54 - column 6, line 39, column 6, line 52 - line 55, figure 1,4 --	1-9
A	GB 1502677 A (INSTRUMENTATION LABORATORY INCORPORATED), 1 March 1978 (01.03.78), page 1, line 70 - line 93; page 2, line 84 - line 96; page 3, line 92 - line 104, figure 1 --	1-9
A	US 4325913 A (STEPHEN C. WARDLAW), 20 April 1982 (20.04.82), figure 1, abstract --	9

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
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"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 December 1995	08 -01- 1996
Name and mailing address f the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized ficer Gunnel Wästerlid Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

11/12/95

International application No.
PCT/SE 95/01038

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		AU-A- 2116883	24/05/84
		CA-A- 1238900	05/07/88
		DE-A- 3375324	18/02/88
		EP-A,B- 0109278	23/05/84
		SE-T3- 0109278	
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		DE-A- 2521061	02/01/76
		FR-A,B,B 2271557	12/12/75
		JP-A- 50147984	27/11/75
		LU-A- 72116	20/08/75
		NL-A- 7503490	17/11/75
		US-A- 3949615	13/04/76
US-A- 4325913	20/04/82	NONE	